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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,533	06/30/2004	Gregory J Mazzola	P51318	4307

20462 7590 07/10/2007

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	
MAIL DATE	**DELIVERY MODE**
07/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,533	MAZZOLA ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,10-12 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *2, 10-12, 14* is/are allowed.

6)☒ Claim(s) *1,3-5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 4/17/07 is acknowledged and has been entered.

Claims 1-5, 7, 10-12 and 14 are presently being examined.

2. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of PCT/US03/00205, *i.e.,* 1/2/03, as the parent provisional application does not support the claimed limitations of the instant application, for example, it does not disclose the pH range recited in instant claim 1 "at about pH 5.0 to about pH 8.0", nor the limitation "in a solvent comprising dimethylacetamide."

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20040213791 A1 in view of Kalyanpur (Molec. Biotechn. 1: 87-98, 2002), Harlow and Lane (Antibodies A Laboratory Manual, 1988, Cold Spring Harbor Laboratory, USA, pages 306-307) and U.S. Patent No. 6,290958 B1.

US 20040213791 A1 discloses a method for preparing an antibody-DM1 maytansinoid conjugate, said method comprising modifying an antibody with SSP at pH 6.0, separating the modified antibody using gel filtration chromatography, conjugating the modified antibody with DM1 in a solvent comprising DMA (*i.e.,* in dimethylacetamide), and separating the conjugate from the unreacted DM1 using gel filtration chromatography and then concentrated using tangential flow filtration.
US 20040213791 A1 further discloses that the yield after the second gel filtration is between 60%-65%. US 20040213791 A1 discloses that tangential flow filtration (TFF) is used to concentrate the antibody prior to reaction with SSP (especially [0656]-[0660]).

US 20040213791 A1 does not disclose wherein the modified antibody is separated from the unreacted SSP linker using tangential flow filtration, nor wherein the conjugate is purified using ion exchange chromatography, including on a ceramic hydroxyapatite column.

Kalyanpur teaches that gel filtration is a technique that is widely employed in biochemical research to purify small quantities of proteins based upon their size (section 3.7). Kalyanpur further teaches that tangential flow filtration (TFF) is the most commonly used method in downstream processing applications in the separation of biomolecules of different sizes (section 2.4). Kalyanpur teaches that TFF is used to concentrate proteins and other large molecules in aqueous streams with the simultaneous removal of the lower-molecular-weight species, salts and water (section 3.2, first sentence). Kalyanpur teach that the yield of a desired protein in each step is critical because even a small product loss in each purification step adds up to significant losses over the entire downstream process, especially if several purification steps are required to reach a high level of purity. The techniques employed usually fall into two major groups, membrane based methods such as TFF and a variety of chromatography procedures (section 3). Kalyanpur teach that use of TFF is compatible with large batch processing (section 2.5). Kalyanpur also teach that ion exchange chromatography is relatively inexpensive, is widely used in the purification of biomolecules, has a high resolving power and capacity, and can be used for the purification of almost any charged molecule that is soluble in an aqueous system (section 3.5). Kalyanpur teaches that well developed processes at the research bench scale are carefully scaled up to the production level, always bearing in mind that fewer the steps used, higher is the eventual yield, even if a particular step only loses 5% of the product (paragraph spanning pages 95-96).

Harlow and Lane teach that antibodies can by purified by a simple column chromatography procedure on hydroxyapatite (HA). Harlow and Lane further teach that the procedure is rapid, applicable to large-scale separations, requires no modification of the sample before loading, provides high yield, and provides high purity when the antibodies are not mixed with other proteins such as BSA (pages 306-307).

U.S. Patent No. 6,290958 B1 discloses that antibodies may be purified on a commercially prepared ceramic hydroxyapatite column (especially detailed description of the text).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used TFF by itself to separate the unreacted linker from the modified antibody and to have used ion exchange chromatography to purify the conjugate, including using the hydroxyapatite column taught by Harlow and Lane or the commercially prepared ceramic hydroxyapatite column disclosed by U.S. Patent No. 6,290958 B1. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a pH of about 6.0 for the conjugation step.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to scale up production of the antibody-DM1 conjugate using methods compatible with large scale production and to simplify purification and increase yield because: (1) US 20040213791 A1 discloses using TFF to concentrate the antibody or antibody-conjugate, and Kalyanpur teaches that TFF is used to concentrate proteins and other large molecules in aqueous streams with the simultaneous removal of the lower-molecular-weight species, salts and water, (2) Kalyanpur teaches that gel filtration is a technique that is widely employed in biochemical research to purify small quantities of proteins, but that use of TFF is compatible with large batch processing and is the most commonly used method in downstream processing applications in the separation of biomolecules of different sizes, (3) US 20040213791 A1 discloses large losses at the step of purification of antibody conjugate using gel filtration chromatography, Harlow and Lane teach that antibodies can by purified by a simple column chromatography procedure on hydroxyapatite (HA) and that the procedure is rapid, applicable to large-scale separations, requires no modification of the sample before loading, provides high yield, and provides high purity when the antibodies are not mixed with other proteins such as BSA (as is the case of the antibody conjugate mixed with unreacted DM1), U.S. Patent No. 6,290958 B1 discloses a commercially available ceramic hydroxyapatite column, and Kalyanpur also teach that ion echange chromatography is relatively inexpensive, is widely used in the purification of biomolecules, has a high resolving power and capacity, and can be used for the purification of almost any charged molecule that is soluble in an aqueous system, (4) Kalyanpur teach that the yield of a desired protein in each step is critical because even a small product loss in each purification step adds up to significant losses over the entire downstream process, especially if several purification steps are required to reach a high level of purity. The techniques employed usually fall into two major groups, membrane based methods such as TFF and a variety of chromatography procedures, and US 20040213791 A1 discloses a large loss using gel filtration as the purification step for the antibody conjugate. One of ordinary skill in the art at the time the invention was made would have been motivated to use a pH of about 6.0 for the conjugation step because US 20040213791 A1 discloses that pH of about 6.0 is compatible with the prior step of linking the antibody to the SSP linker and because pH 6.0 is a mild condition.

5. Claims 1, 3-5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20040213791 A1 in view of Kalyanpur (Molec. Biotechn. 1: 87-98, 2002), Harlow and Lane (Antibodies A Laboratory Manual, 1988, Cold Spring Harbor Laboratory, USA, pages 306-307), U.S. Patent No. 6,290958 B1 and Chari *et al* (Cancer Research. 1992, 52: 127-131).

US 20040213791 A1 discloses a method for preparing an antibody-DM1 maytansinoid conjugate, said method comprising modifying an antibody with SSP at pH 6.0, separating the modified antibody using gel filtration chromatography, conjugating the modified antibody with DM1 in a solvent comprising DMA (*i.e.,* in dimethylacetamide), and separating the conjugate from the unreacted DM1 using gel filtration chromatography and then concentrated using tangential flow filtration.
US 20040213791 A1 further discloses that the yield after the second gel filtration is between 60%-65%. US 20040213791 A1 discloses that tangential flow filtration (TFF) is used to concentrate the antibody prior to reaction with SSP (especially [0656]-[0660]).

US 20040213791 A1 does not disclose wherein the modified antibody is separated from the unreacted SSP linker using tangential flow filtration, nor wherein the conjugate is purified using ion exchange chromatography, including on a ceramic hydroxyapatite column.

Kalyanpur teaches that gel filtration is a technique that is widely employed in biochemical research to purify small quantities of proteins based upon their size (section 3.7). Kalyanpur further teaches that tangential flow filtration (TFF) is the most commonly used method in downstream processing applications in the separation of biomolecules of different sizes (section 2.4). Kalyanpur teaches that TFF is used to concentrate proteins and other large molecules in aqueous streams with the simultaneous removal of the lower-molecular-weight species, salts and water (section 3.2, first sentence). Kalyanpur teach that the yield of a desired protein in each step is critical because even a small product loss in each purification step adds up to significant losses over the entire downstream process, especially if several purification steps are required to reach a high level of purity. The techniques employed usually fall into two major groups, membrane based methods such as TFF and a variety of chromatography procedures (section 3). Kalyanpur teach that use of TFF is compatible with large batch processing (section 2.5). Kalyanpur also teach that ion exchange chromatography is relatively inexpensive, is widely used in the purification of biomolecules, has a high resolving power and capacity, and can be used for the purification of almost any charged molecule that is soluble in an aqueous system (section 3.5). Kalyanpur teaches that well developed processes at the research bench scale are carefully scaled up to the production level, always bearing in mind that fewer the steps used, higher is the eventual yield, even if a particular step only loses 5% of the product (paragraph spanning pages 95-96).

Harlow and Lane teach that antibodies can by purified by a simple column chromatography procedure on hydroxyapatite (HA). Harlow and Lane further teach that the procedure is rapid, applicable to large-scale separations, requires no modification of the sample before loading, provides high yield, and provides high purity when the antibodies are not mixed with other proteins such as BSA (pages 306-307).

U.S. Patent No. 6,290958 B1 discloses that antibodies may be purified on a commercially prepared ceramic hydroxyapatite column (especially detailed description of the text).

Chari *et al* teach conjugation of maytansinoids to antibodies linked to SSP at pH 7.0.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used TFF by itself to separate the unreacted linker from the modified antibody and to have used ion exchange chromatography to purify the conjugate, including using the hydroxyapatite column taught by Harlow and Lane or the commercially prepared ceramic hydroxyapatite column disclosed by U.S. Patent No. 6,290958 B1. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a pH of about 7.0 for the conjugation step as taught by Chari *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to scale up production of the antibody-DM1 conjugate using methods compatible with large scale production and to simplify purification and increase yield because: (1) US 20040213791 A1 discloses using TFF to concentrate the antibody or antibody-conjugate, and Kalyanpur teaches that TFF is used to concentrate proteins and other large molecules in aqueous streams with the simultaneous removal of the lower-molecular-weight species, salts and water, (2) Kalyanpur teaches that gel filtration is a technique that is widely employed in biochemical research to purify small quantities of proteins, but that use of TFF is compatible with large batch processing and is the most commonly used method in downstream processing applications in the separation of biomolecules of different sizes, (3) US 20040213791 A1 discloses large losses at the step of purification of antibody conjugate using gel filtration chromatography, Harlow and Lane teach that antibodies can by purified by a simple column chromatography procedure on hydroxyapatite (HA) and that the procedure is rapid, applicable to large-scale separations, requires no modification of the sample before loading, provides high yield, and provides high purity when the antibodies are not mixed with other proteins such as BSA (as is the case of the antibody conjugate mixed with unreacted DM1), U.S. Patent No. 6,290958 B1 discloses a commercially available ceramic hydroxyapatite column, and Kalyanpur also teach that ion echange chromatography is relatively inexpensive, is widely used in the purification of biomolecules, has a high resolving power and capacity, and can be used for the purification of almost any charged molecule that is soluble in an aqueous system, (4) Kalyanpur teach that the yield of a desired protein in each step is critical because even

a small product loss in each purification step adds up to significant losses over the entire downstream process, especially if several purification steps are required to reach a high level of purity. The techniques employed usually fall into two major groups, membrane based methods such as TFF and a variety of chromatography procedures, and US 20040213791 A1 discloses a large loss using gel filtration as the purification step for the antibody conjugate. One of ordinary skill in the art at the time the invention was made would have been motivated to use a pH of around 6.0 to around 7.0 for the conjugation step because US 20040213791 A1 discloses that pH of about 6.0 is compatible with the prior step of linking the antibody to the SSP linker, Chari *et al* teach a conjugation step at pH 7.0, and because pH 6.0-pH 7.0 is a mild condition.

6. Claims 2, 10-12 and 14 appear to be free of the prior art.

7. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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